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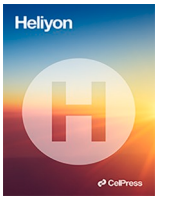

Review article

A comprehensive review of transduction methods of lectin-based biosensors in biomedical applications

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ABSTRACT

Biosensors have emerged as a pivotal technology in the biomedical field, significantly enhancing the rapidity and precision of biomolecule detection. These advancements are instrumental in refining diagnostic processes, optimizing treatments, and monitoring diseases more effectively. Central to the development of highly sensitive, selective, and stable biosensors are the bioreceptor and transducer components. This review paper discusses the use of lectin as a bioreceptor and explores the prevalent transducer methods employed in lectin-based biosensors, with a particular emphasis on their applications in biomedical research. The paper meticulously examines various transducers, with a spotlight on electrochemical and optical transduction methods, drawing from a wealth of previous studies to offer a comprehensive perspective on the application of these sensors in critical biomedical areas. These areas include early diagnosis, therapeutic interventions, and continuous health monitoring. Moreover, the review addresses the challenges of implementing lectin-based biosensors, such as specificity and stability issues. It also explores future possibilities, examining potential trends to overcome these challenges. In summary, this comprehensive analysis aspires to equip researchers with profound insights into the transformative potential of lectin-based biosensors, underscoring their significant role in the evolution of biomedical research and the broader healthcare landscape.

1. Introduction

Since their inception in the 1960s, biosensors have become increasingly important in various sectors, such as healthcare, environmental monitoring, industry, food safety, and agriculture [1–5]. Their application in healthcare is most prominent, where they are used for self-monitoring (e.g., glucose and lactic acid levels [6–8]), detecting pathogens (e.g., bacteria and viruses [9–11]), and identifying disease biomarkers (e.g., for cancer [12], cardiovascular diseases [13], and hormone-related conditions [14,15]). Those common uses are due to biosensors offering several advantages over traditional methods of biological detection, such as bacterial culturing or conventional PCR, which are generally labor-intensive and time-consuming. Some of the main advantages include high sensitivity, stability, and selectivity. Biosensors are also efficient, cost-effective, fast real-time detection, user-friendly, and straightforward to use [16].

The International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor as a device that employs specific biochemical

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reactions facilitated by isolated enzymes, immunosystems, tissues, organelles, or whole cells to identify chemical compounds typically achieved through electrical, thermal, or optical signals [1,17]. A biosensor comprises four main parts: an analyte, a bioreceptor, a transducer, and a signal processor, including the display unit, as shown in Fig. 1. The bioreceptor selectively identifies the analyte of interest through specific interactions. It can be enzyme, DNA, RNA, antibody, etc. The transducer transforms the biochemical interaction into a signal that can be measured. Typically, it can induce a change in mass, conductivity, electrochemical properties, or optical properties. The process of creating a biosensor involves the design of a bioreceptor for targeted analytes, the fabrication of the transducer, including the preparation of the sensing material, the immobilization of bioreceptors onto this material, and the testing of the sensing platform using a system that processes the physio-chemical signal [18].

Selecting a bioreceptor is crucial for determining the biosensor's sensitivity and specificity. Among these choices, lectins, known for their specific sugar-binding capabilities, are emerging as a notable choice for bioreceptors for their ability to recognize many biomarkers. Lectins exist in various organisms, including plants, animals, algae, fungi, yeast, bacteria, and viruses. These proteins or glycoproteins can bind selectively to glycan structures, which allows for the precise detection of analytes due to their recognition of complex glycan patterns on biomolecules [19]. Lectins can also identify and bind to glycans found within cells, attached to cell membranes, or secreted into biological fluids. They play a role in cell-cell and host-pathogen interactions by recognizing and binding to the surface carbohydrates of other cells. These interactions are non-enzymatic as the binding of lectins to specific glycans is reversible and occurs through hydrogen bonds, metal coordination, van der Waals, and hydrophobic interactions without altering the glycan structure during binding. For example, some lectins and their associated biomarkers include agglutinin and concanavalin A (ConA), which can detect carcinoembryonic antigen N-glycan. Additionally, ConA, Wheat Germ Agglutinin (WGA), and Ulex europaeus agglutinin (UEA) can specifically identify carbohydrates in *E. coli* and *S. aureus* bacteria [9,20,21]. This unique capability makes lectins suitable for various biosensors with high speed, sensitivity, stability, and cost-effectiveness, serving diverse purposes such as glucose determination, detection of whole bacteria or viruses, and identification of cancer biomarkers.

This study aims to provide a detailed review and analysis of different transducers used in lectin-based biosensors, emphasizing their biomedical applications. Fig. 2 shows three common types of transducers that will be reviewed in this paper, including electrochemical (Electrochemical impedance spectroscopy, Voltammetry, Amperometry), optical (Surface plasmon resonance, Fluorescence-based, Colorimetry, etc.), and others (Quartz crystal microbalance, microfluidic biosensors). Primarily, this paper examines electrochemical and optical sensing methods to offer an in-depth understanding of the role of lectins in the innovation of biosensing technologies. The study seeks to elucidate the basic principles behind lectin-ligand interactions and their incorporation into electrochemical and optical biosensors. The review intends to highlight the advantages and drawbacks of lectin-based methods within biomedical research by exploring the latest research, case studies, and new technologies. This work stands out from previous reviews by providing a broader perspective on transducers and lectin types in biomedical applications, supported by the latest databases. In contrast, earlier reviews were more narrowly focused scopes. For instance, Silva's review, "Lectin-based biosensors as analytical tools for clinical oncology" [22], is concentrated on the use of lectin-based biosensors specifically in oncology, highlighting cancer glycobiomarkers. Similarly, Wang's review, "Recent Progress in Lectin-Based Biosensors" [23], primarily discusses the applications of lectin-based biosensors in glucose sensing, pathogen detection, cytosensing, and toxin sensing. A 2021 systematic review [24] focuses on electrochemical biosensors for clinically relevant carbohydrates and glycoconjugates, while Vishweswaraiah's 2022 review, "Monitoring of Microbial Safety of Foods Using Lectins", covers lectin applications in food safety, with only a brief discussion on

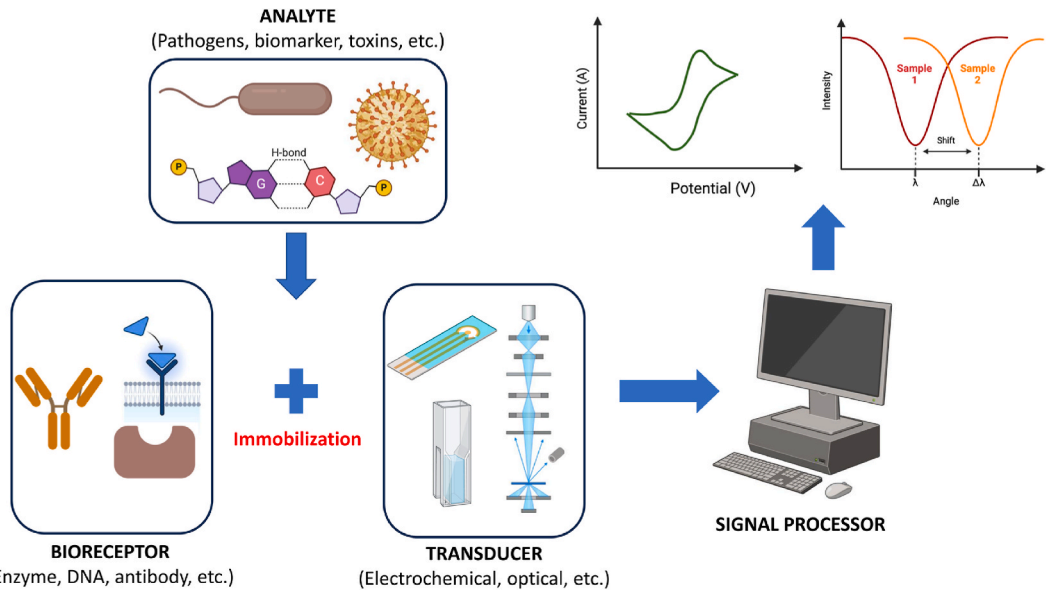

Fig. 1. Components of a typical biosensor include bioreceptors (such as enzymes, probes, aptamers, antibodies, etc.), transducers (electrochemical, optical, etc.), and signal processors.

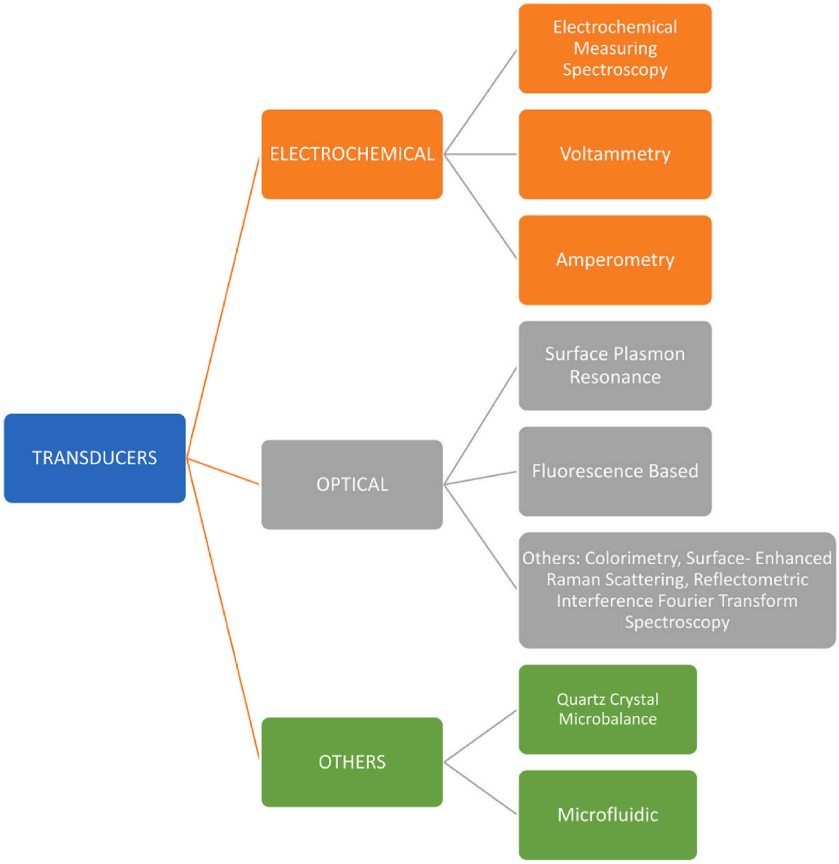

Fig. 2. Different transducers are used in lectin-based biosensors for biomedical applications.

biosensors [25]. Furthermore, Echeverri's 2022 review, "Glycan-Based Electrochemical Biosensors", narrows its focus to electrochemical glycobiosensors for infectious diseases and cancer biomarkers, particularly colorectal cancer [26]. Finally, Dan's 2010 review, "Development and Applications of Lectins as Biological tools in biomedical research", provides an overview of lectins' biological functions and applications in biomedical research but lacks recent data and focuses more broadly on lectins' roles beyond biosensors [27]. Thus, this review fills a unique gap by addressing a comprehensive range of transducer methods and lectins used in biomedical applications, positioning itself as a more encompassing and up-to-date resource in this field. Overall, this comprehensive analysis aims to foster progress in biosensor technology and aid in developing sophisticated diagnostic tools for essential biomedical uses.

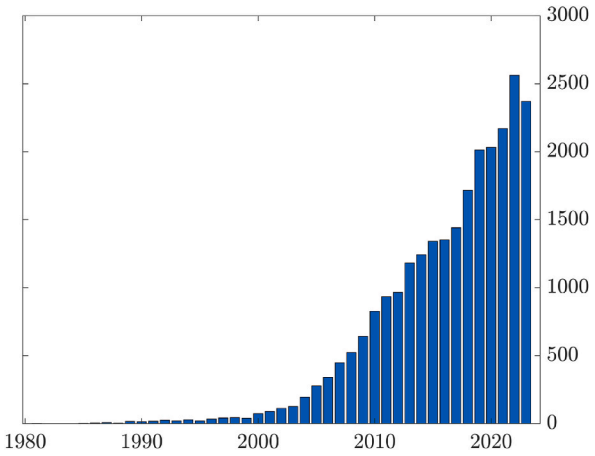

Fig. 3. Studies related to electrochemical biosensors over the years (PubMed).

2. Electrochemical lectin-based biosensors

In 1962, Clark and Lyons developed the first electrochemical biosensor to monitor glucose concentration [28]. Since then, various electrochemical sensors for detecting multiple biomolecules (cancer biomarkers, proteins, carbohydrates, bacteria, viruses, etc.) have been reported (Fig. 3). Among different types of biosensors, the electrochemical biosensor is typically recommended in clinical settings because it requires simple instrumentation, is capable of being miniaturized as a cost-effective, and highly sensitive point-of-care device [29]. Electrochemical sensing typically involves a working electrode, a reference electrode, and a counter or auxiliary electrode within an electrolyte medium. The working electrode acts as the transduction element where biochemical reactions occur. The counter electrode facilitates the application of a current to the working electrode *via* an electrolytic medium. During the redox reaction at the electrode's surface, electrons are transferred between the analyte and the working electrode [30].

Fundamental electrochemical biosensors are categorized based on signal transduction mechanism: electrochemical impedance spectroscopy (EIS), voltammetry, amperometry, potentiometry, and conductometry [31], as illustrated partly in Fig. 4. A potentiostat system commonly employs a three-electrode format, as described above. Meanwhile, a two-electrode format (working and auxiliary) is often used for conductometry and EIS [32]. Electrodes can be fabricated from different materials using various manufacturing processes. The materials can be conducted or semiconducted, including metals (such as gold) or nonmetals (such as carbon). The manufacturing process will directly influence the electrode size in bulk, micro- or nanostructures. Essentially, the material choices and fabrication approach will ultimately determine the biosensor's efficiency and performance, which can be showcased through sensitivity, selectivity, detection range, and limit of detection (LOD).

For lectin-based biosensors, different materials have been used as the sensing platform of the system, as shown in Table 1. The transduction methods are commonly EIS, voltammetry, and amperometry, which will be described in more detail in the following sections.

2.1. Electrochemical impedance spectroscopy (EIS)

EIS is typically the most widely used due to the possibility of monitoring the biorecognition reaction occurring on the modified electrode's surface without a label [31]. In electrochemical impedance, the cell's current is measured by an AC potential to an electrochemical cell. The impedance measures the impeded flow of ions through solutions, interfaces, and coatings [41]. By the variation of the frequency of the applied potentials, the impedance of the modified surface can be calculated and fitted with a Randles electrical equivalent circuit, as shown as an example in Fig. 5(a and b). Based on the fitted electrical components, the analytes with unknown concentrations were determined [42]. Impedance methods are powerful because they can sample electron transfer at high frequencies and mass transfer at low frequencies [43].

Table 1 shows some recent publications of lectin-based sensors with EIS measurements. For example, Silva et al. used glutaraldehyde to self-assemble ConA lectin on steel electrodes modified with polyaniline (PANI) thin films through covalent binding **to detect** *Escherichia coli* and *Staphylococcus aureus*. This sensor has a limit of detection (LOD) of only 50 μg/mL, as illustrated in Fig. 6 [33]. The goal is to detect specific bacterial toxins of the two mentioned bacteria, namely lipopolysaccharide (LPS) from Escherichia coli and lipoteichoic acid from Staphylococcus aureus. The EIS results showed that the resistance charge transfer (R_{CT}) of the electrode/electrolyte interface increases significantly when there is an interaction between ConA and specific carbohydrate moieties in the bacterial toxins. In different works, bacteria and ConA can also detect various types of viruses [10]. Cysteine (Cys), zinc oxide nanoparticles (ZnONp), and ConA lectin were used to differentiate between arboviruses infections induced by multiple types of viruses,

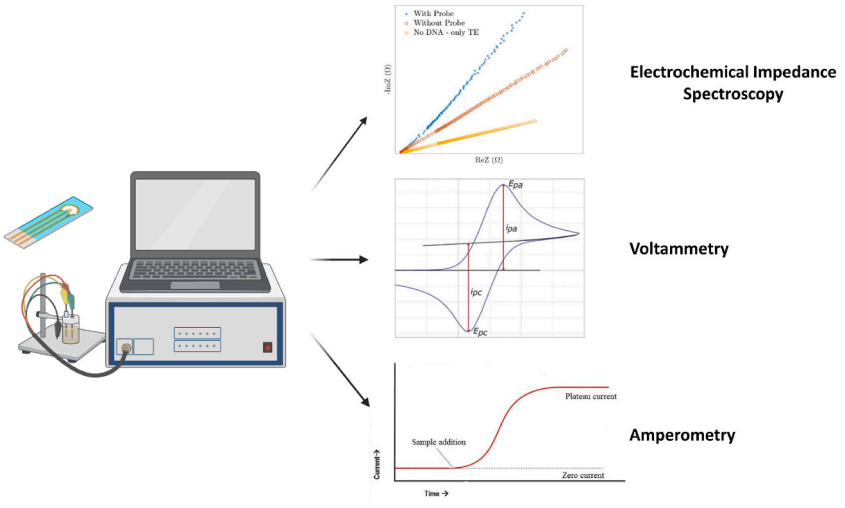

Fig. 4. A typical setup for electrochemical-based biosensors. The graph shows examples of EIS, cyclic voltammetry, and amperometry measurements.

Table 1
Electrochemical measuring methods applied in lectin-based biosensors.

Electrochemical methods	Sensing platform	Application	Target	Lectin	Limit of detection (LOD)	Detection range	Ref
EIS	electro synthesized polyaniline (PANI)	Bacteria detection	*Escherichia coli* and *Staphylococcus aureus*	ConA	50 μg/mL	50 μg/mL - 200 μg/mL	[33]
EIS	zinc oxide nanoparticles (ZnONp)	Virus detection	DENV2, ZIKV, CHIKV, and YFV	ConA	0.0421 pfu mL^{-1} for ZIKV, 0.0437 pfu mL^{-1} for YFV, 0.062 pfu mL^{-1} for CHIKV, and 0.0382 pfu mL^{-1} for DENV	NA	[10]
EIS	Gold electrode	Fungi detection	Candida spp.	ConA, WGA	10^2 CFU mL^{-1} (*C. krusei*)	10^2–10^6 CFU mL^{-1}	[34]
EIS	Streptavidin gold nanoparticles (GNP)	rheumatoid arthritis, inflammatory bowel disease, and many cancers	Galactosylation of IgG	GSL II, RCA I	0.031 μg/μl	0.1^{-1} μg/μl	[35]
EIS	nitrogen-doped graphene quantum dots (NGQDs)	Breast cancer cell detection	MCF-7	PHA-L	1 cell mL^{-1} in PBS and 2 cells mL^{-1} in human serum	5 to 10^6 cells mL^{-1} in PBS and 20–10^6 cells mL^{-1} in human serum	[12]
Cyclic voltammetry + EIS	lubricin-peanut agglutinin (LUB-PNA) interface	Cancer biomarkers detection	cancer-associated glycoprotein (asialofetuin, ASF)	PNA	39 nM in PBS	39 nM to 2.5 μM	[36]
Cyclic voltammetry + amperometry	gold/platinum hybrid functionalized zinc oxide nanorods (Pt-Au@ZnONRs)	Glucose detection	glucose	ConA	0.6 μM	1.8 μM to 5.15 mM	[37]
Amperometry	multi-walled carbon nanotubes (MWCNTs)	Glucose detection	glucose	ConA	0.31 μM	2.0×10^{-6} M to 4.1×10^{-4} M	[38]
Amperometry	Fe_3O_4@SiO_2 nanoparticles	Breast cancer cell detection	MCF-7 cells	ConA	30 cells mL^{-1}	100 to 10^6 cells mL^{-1}	[39]
Amperometry	polydopamine film	Glucose detection	D-glucose	ConA	7.5×10^{-7} M	1.0×10^{-6} to 1.0×10^{-4} M	[40]

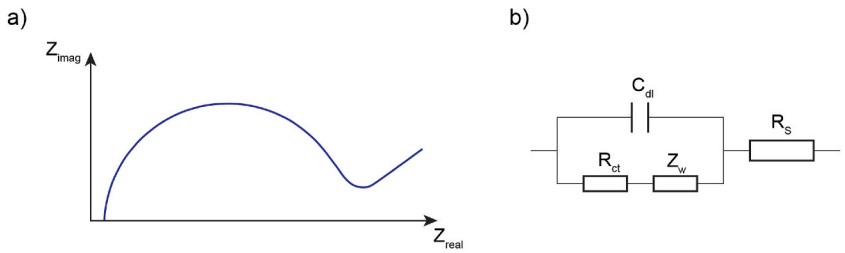

Fig. 5. (a) A Nyquist plot shows the relationship between the imaginary and real parts of impedance as the frequency changes. (b) A Randles electrical equivalent circuit fits the Nyquist plot in (a) based on EIS measurements. The electrical components include solution resistance (R_s), charge transfer resistance (R_{ct}), the Warburg element represents the diffusive process (Z_w), and double-layer capacitor (C_{dl}).

including Dengue type 2 (DENV2), Zika (ZIKV), Chikungunya (CHIKV), and Yellow fever (YFV). This high sensitivity and selectivity are due to the inhibition of the redox process associated with the formation of the Cys-ZnONp-ConA complex on the electroactive surface and its subsequent interaction with viral glycoproteins. Especially, ConA lectin identifies the structural glycoproteins of DENV2, ZIKV, CHIKV, and YFV, with DENV2 being the most structurally similar to ZIKV.

With the ability to detect many analytes, as discussed, EIS lectin-based biosensors may also have a wide range of applications based on the different lectins used. Tran et al. has successfully developed an ultrasensitive electrochemical sensor fabricated from nitrogen-doped graphene quantum dots (NGQDs) and phytohemagglutinin-L (PHA-L) lectin onto screen-printed electrodes (SE) for the detection of breast cancer cells MCF-7 [12]. This highly selective detection of MCF-7 is due to the dual-functionalized NGQDs, which can not only improve the electrical conductivity but also act as nanocarriers for PHA-L, which is a specific receptor for MCF-7. Hence, the sensor exhibited a linear response within the detection range of 5 to 10^6 cells mL^{-1} in phosphate-buffered saline (PBS) and 20–10^6 cells mL^{-1} in human serum. Especially, the sensor showcased excellent sensitivity with extremely low detection limits of 1 cell mL^{-1} in PBS and 2 cells mL^{-1} **in human serum.**

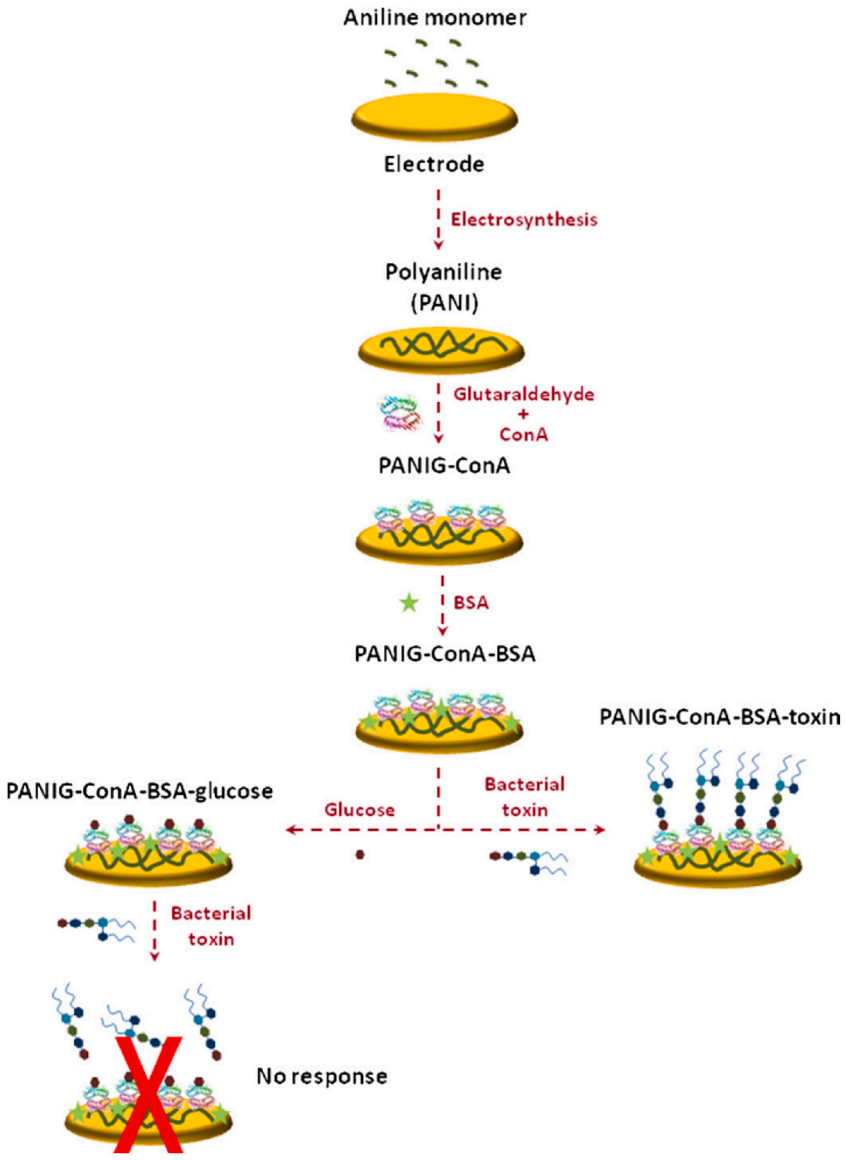

Fig. 6. Schematic representation of the fabrication process of the PANI-modified sensor for detecting bacterial toxins. Reproduced with permission from Elsevier, order number 5742821296918 [33].

Furthermore, the EIS lectin-based biosensor **also has superior selectivity and long-term stability, making it a highly efficient sensing platform for early diagnosis and treatment of** various diseases. For example, galactosylation of immunoglobulin G (IgG) was recently suggested as a potential biomarker for rheumatoid arthritis, inflammatory bowel disease, and many cancers [44–46]. **Khorshed et al.** proposed a portable impedance-based biosensor that utilizes lectin array technology to detect glycans in immunoglobulin G (IgG) [35]. This biosensor chip was modified with IgG, streptavidine gold nanoparticles, and 2 types of lectin: biotinylated Griffonia simplicifolia (GSL II) and Ricinus communis agglutinin I (RCA I). These 2 lectins were used to determine the ratio of N-acetyl glucosamine (GlcNAc) to galactose (Gal), respectively, namely the agalactosylation level (AF). Determining the ratio of GSL II lectin response to RCA I lectin (AF) yields a distinct value for each species and the severity of diseases. This technique was effectively employed to differentiate between rat and human IgG galactosylation levels, achieving a detection limit of 0.031 μg/μL for IgG. Moreover, this biosensor also has potential applications in diagnosing COVID-19.

In another study, ConA was used with wheat germ agglutinin (WGA) lectin to detect *Candida species* [34]. The bare gold working electrodes were modified with cysteine, gold nanoparticles (MBA-AuNPs), and either ConA or WGA acting as the bioreceptors which recognize the yeast cells. In this work, Atomic Force Microscopy images show alterations in the biosensor surface following the assembly of molecules and exposure to fungal samples. Meanwhile, the EIS analysis revealed a proportional charge transfer resistance (R_{CT}) increase as fungal CFU increased. The detection range was 10^2–10^6 CFU mL^{-1}, with an LOD of 10^2 CFU mL^{-1} for *Candida species*.

Overall, EIS lectin-based biosensors present a promising approach for biomedical applications due to their high sensitivity, specificity, and ability to detect a wide range of biological molecules, such as glycoproteins found on the surface of pathogens and cancer cells. However, despite these advantages, there are several challenges and limitations associated with EIS lectin-based biosensors. The main concern lies in the stability and reproducibility of lectin immobilization on the sensor surface, which can affect the sensor's performance over time. Additionally, the specificity of lectins to their target glycans can sometimes be compromised by the presence of structurally similar molecules, potentially leading to false-positive or false-negative results. Moreover, the integration of these biosensors into practical biomedical devices requires careful consideration of factors such as response time, scalability, and the ability to operate in complex biological matrices. Therefore, while EIS lectin-based biosensors hold significant potential for advancing diagnostics and therapeutic monitoring, further research is needed to address these challenges and enhance their practical applicability in clinical settings.

2.2. Voltammetry

Voltammetric sensors are derived from controlled potential techniques, which apply a known potential and measure the resultant current. Current–potential relationships are represented graphically by a voltammogram, marked by a peak current that occurs at the redox potential of the target analyte, the magnitude of which is discretely proportional to the bulk concentration of the active species [47]. In voltammetry, redox peaks on a voltammogram can be influenced by factors beyond the target analyte. While the analyte typically generates the main peaks, the electrode material may also contribute additional peaks or background currents due to its own redox reactions. Capacitive currents from the electrode-electrolyte interface, as well as impurities or side reactions, can further obscure the analyte signals. Additionally, interactions between the analyte and the electrode surface can alter the shape, position, or height of the peaks. To illustrate redox reactions in voltammetry, we can refer to an example from previous work [48]. This example shows the charge storage phenomenon in MoS_2 with a KOH electrolyte, which can be generalized by two mechanisms: the double-layer mechanism $(MoS_2)_{surface} + K^+ \leftrightarrow (MoS_2 - K^+)_{surface}$ and the Faradaic mechanism $MoS_2 + K^+ + e^- \leftrightarrow MoS - SK^+$. Overall, redox peaks reflect both the behavior of the analytes and the influence of the electrode material and other factors. If the difference between redox potentials is sufficient, simultaneous detection of multiple analytes is possible within a single potential sweep. Various distinct voltammetric techniques have been developed through variations of the pattern of applied potential to the surface. Of the existing voltammetric techniques, cyclic voltammetry (CV) is the simplest and most widely used, and it is the first experiment to characterize an electrochemically active material [48–50]. In CV, the potential is ramped linearly in a triangular waveform between two potential values that can be repeated over multiple cycles [51].

Recently, Li et al. proposed a lubricin-peanut agglutinin (LUB-PNA) interface for monitoring glycan binding interactions to detect

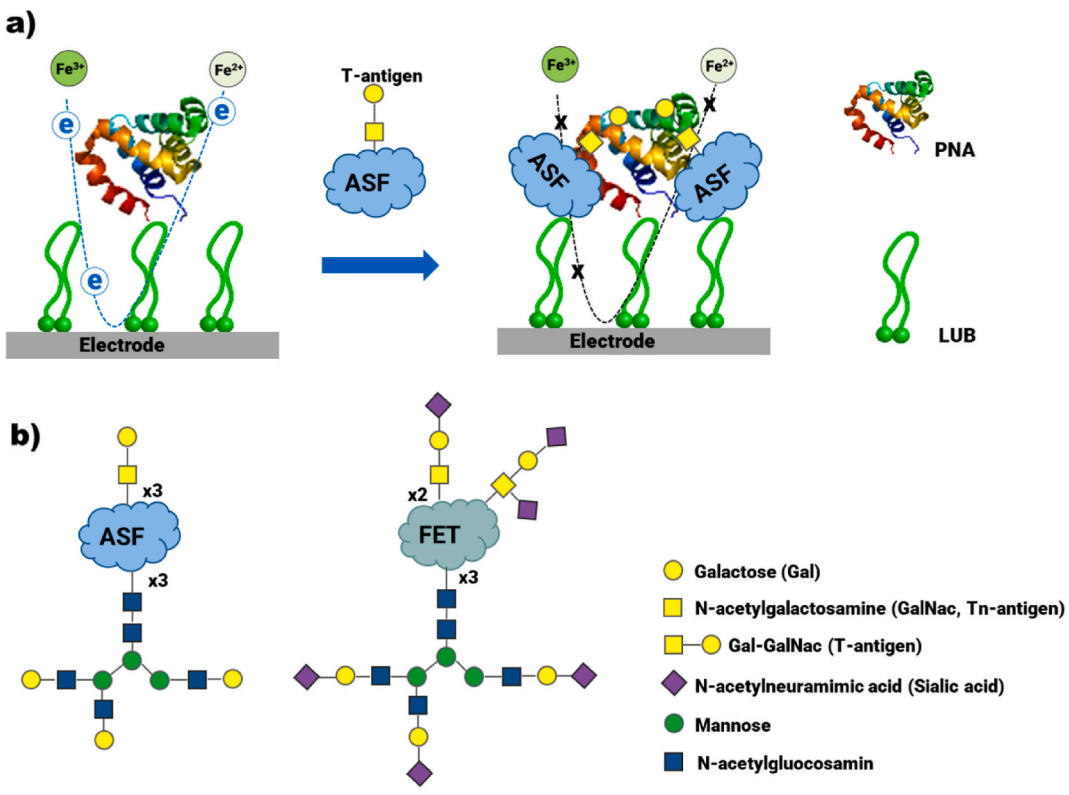

Fig. 7. Schematic illustrations of the assay used in CV measurement in Ref. [36]. Elsevier permission is not required.

a cancer-associated glycoprotein, specifically asialofetuin (ASF) [36]. With ferricyanide as the electrochemical mediator in Fig. 7(a and b), CV and EIS measurements were conducted to characterize the surface modification and the sensor response to the target analytes [36]. The CV response of the LUB-PNA electrode indicated high specificity towards the sensor's ASF. Quantitative detection of ASF was also investigated, and the results exhibited good linearity in the calibration parameters (oxidation peak current, reduction peak current, and the peak-to-peak separation of ferricyanide) against the logarithm form of the ASF concentrations within a detection range from 39 nM to 2.5 μM and limit of detection of 39 nM, the lowest concentration detected experimentally.

In another study, CV was also used by Zhang et al. to build a glucose biosensor based on glucose oxidase – lectin biospecific interaction [37]. To fabricate the biosensor, the surface of glassy carbon electrode (GCE) was modified with gold/platinum hybrid functionalized zinc oxide nanorods (Pt–Au@ZnONRs); proceeded with a layer of porous gold nanocrystals (pAu) film on top; following that ConA was immobilized onto the surface of the pAu film; and finally, the glucose oxidase (GOx) was immobilized on the ConA/pAu/Pt–Au@ZnONRs/GCE by the bispecific interaction between GOx and ConA. A sharp increase of the oxidation current in the CV response in correlation with the addition of glucose indicates the sensor obtained excellent electrocatalytic activity toward glucose from 1.8 μM to 5.15 mM with the LOD of 0.6 μM.

In conclusion, voltammetry offers several advantages, including rapid response times, a wide dynamic range, and the ability to detect low concentrations of analytes. Additionally, voltammetry is particularly well-suited for detecting molecules that undergo redox reactions, providing direct information about the electrochemical properties of the target analyte. Compared to EIS lectin-based biosensors, voltammetry sensors offer faster detection and are generally more straightforward in their operation. While EIS biosensors measure changes in charge transfer resistance and provide information about the overall impedance of the sensor interface, voltammetry sensors are more direct, focusing on current changes related to the oxidation or reduction of the analyte. This can make voltammetry more effective for real-time applications where speed is crucial. However, voltammetry sensors may be less effective than EIS sensors in detecting non-redox-active molecules, limiting their versatility in some applications. In summary, while voltammetry lectin-based sensors offer rapid and straightforward detection for redox-active molecules, EIS lectin-based biosensors provide broader applicability for various biological targets due to their sensitivity to surface changes. The choice between these techniques depends on the specific biomedical application, the nature of the target analyte, and the required sensitivity and speed of detection. For comprehensive diagnostic platforms, integrating both methods could provide complementary advantages, enhancing overall sensor performance and versatility.

2.3. Amperometry

Amperometric devices measure the current related to the redox reaction of an electroactive species in a biochemical reaction as a function of time. The measured current is obtained by maintaining a fixed voltage between the working and the reference electrodes

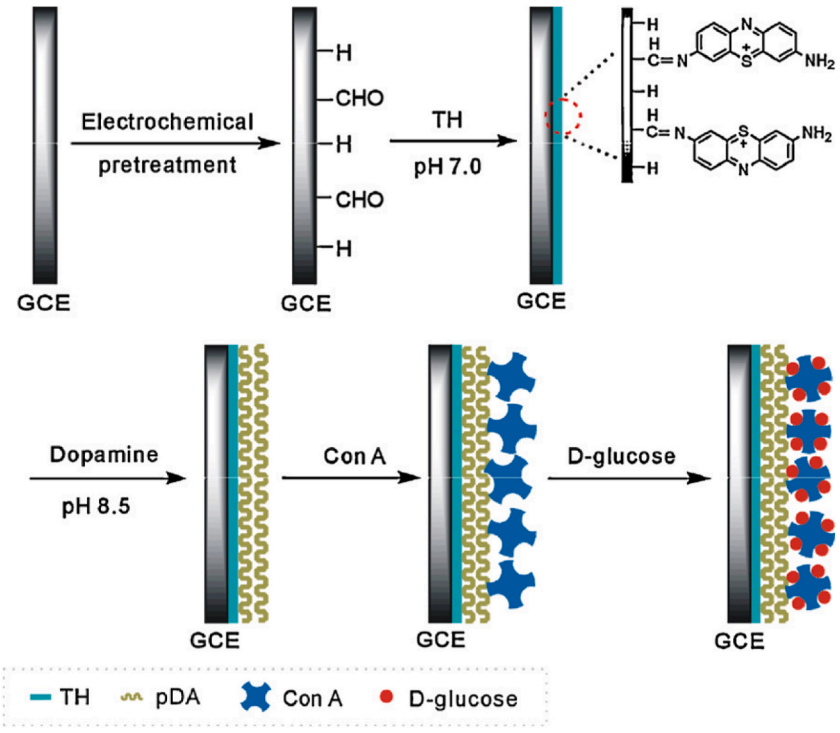

Fig. 8. Schematic of the fabricated glucose amperometric biosensor. Reproduced with permission from Elsevier, order number 5742820093085 [40].

[52]. This type of biosensor is prevalent in the detection of glucose. In the previous study, Li et al. fabricated a non-enzyme glucose amperometric biosensor based on the biospecific binding affinity of ConA for d-glucose (Fig. 8) [40]. The glassy carbon electrode was modified with thionine (TH), followed by the surface-adherent polydopamine film formed by self-polymerization of dopamine attached to TH. Then, ConA was immobilized onto the polydopamine film. The electrochemical behaviors of the glucose biosensor were evaluated by multiple methods: EIS, CV, and amperometry, with amperometry used to determine D-glucose concentrations in different concentrations. The amperometric responses showed that the oxidation current decreased continuously as a function of glucose concentration in the range of 1.0×10^{-6} to 1.0×10^{-4} M. The biosensor also showed excellent sensitivity with a low detection limit of 7.5×10^{-7} M.

Another method involves the non-covalent functionalization of multi-walled carbon nanotubes (MWCNTs) with the lectin ConA, as Ortiz and colleagues showed [38]. In their research, the team suggested using two glycoenzymes, glucose oxidase (GOx) and horseradish peroxidase (HRP), to create mono and bienzymatic glucose biosensors. This biosensor can detect bienzymatic glucose with a sensitivity of (2.22 ± 0.03) μA mM^{-1}, which is 5.2 times higher than that of the mono enzymatic biosensor, and a detection limit of 0.31 μM. The reproducibility was reported at 5.4 %, and when tested with human blood serum, the biosensor demonstrated an excellent correlation with laboratory-reported values.

The application of amperometric lectin-based biosensors is not only limited to glucose sensing. Liu et al. has applied this method to breast cancer cell detection [39]. They developed a non-enzymatic sandwich-structured electrochemical cytosensor based on a cell-specific aptamer, the lectin-functionalized porous core–shell palladium gold nanoparticles (Pd@Au NPs). The cytosensor was fabricated by taking advantage of Pd@Au NPs acting as signal amplification probes and aminating Fe_3O_4@SiO_2 NPs as nanocarriers. The results showed that the catalytic current value has a linear relationship with the logarithmic value of cell concentration ranging from 100 to 1×10^6 cells mL^{-1} with the limit of detection (LOD) down to 30 cells mL^{-1}. The specificity of the established cytosensor was also assessed through the chronoamperometric method. The same method was conducted in mixed cell solution at the same concentrations of MCF-7 and other negative tumor cells, including MCF-10A, MB-MDA-231, and HEK-293T cells, to evaluate the possibility of detecting MCF-7 in multiple cell suspensions. The result was nearly identical to the MCF-7 cell alone, indicating that the established sensor can detect MCF-7 cells in complicated mixtures. In conclusion, this biosensor exhibited a broad linear detection range, excellent sensitivity, and high selectivity.

In summary, amperometric lectin-based biosensors are highly sensitive, offering rapid response times and the capability to detect low concentrations of target analytes, such as glycoproteins found on the surface of pathogens or cancer cells. The main advantage of amperometric sensors is their simplicity and direct measurement approach, which facilitates integration into compact, portable devices for point-of-care diagnostics. However, amperometric biosensors may be limited by the requirement for the target analyte to undergo a redox reaction, which can restrict their use to specific types of molecules and may necessitate the use of mediators to facilitate electron transfer, adding complexity and potential interference. Like voltammetry lectin-based biosensor, when compared to electrochemical impedance spectroscopy (EIS) lectin-based biosensors, amperometric biosensors offer faster response times and simpler operation but may lack the broader applicability of EIS sensors, which can detect a wider range of biomolecules, including those that do not participate in redox reactions. In contrast, voltammetry lectin-based sensors provide a versatile middle ground, offering the ability to detect both redox-active and non-redox-active molecules by analyzing the entire current-potential relationship rather than just the steady-state current. Voltammetry sensors can provide detailed information about the electrochemical properties of the analyte and the sensor interface. However, they may not achieve the same level of simplicity or speed as amperometric sensors or the broad applicability of EIS sensors. Hence, while amperometric lectin-based biosensors are advantageous for their simplicity, speed, and sensitivity in specific applications, they may be less versatile than EIS or voltammetry biosensors. The choice between these biosensing methods depends on the specific requirements of the biomedical application, such as the type of analyte, the desired detection speed, sensitivity, and the complexity of the sample matrix.

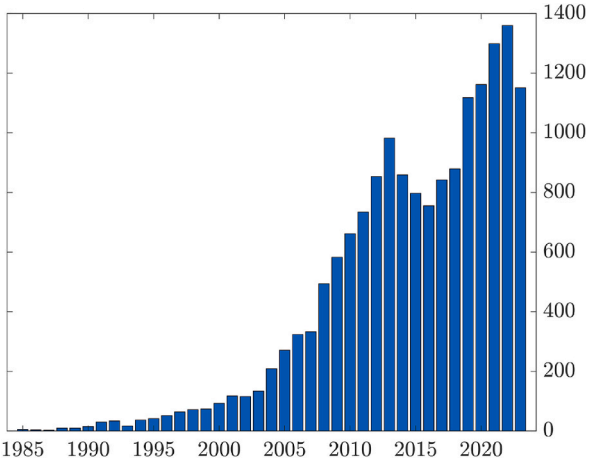

Fig. 9. Studies related to optical biosensors over the years (PubMed).

3. Optical lectin-based biosensors

Besides electrochemical biosensors, optical biosensors have attracted a lot of attention from researchers (Fig. 9). In optical biosensors, the result of the biological recognition event can change the system's absorbance, reflectance, scattering, fluorescence, polarization, or refractive index [53–55]. Optical biosensors offer several advantages over electrochemical methods, including eliminating the need for a reference electrode, immunity to electromagnetic interference, multi-channel/multiparameter detection capability, and compact design. Optical signals also provide high sensitivity, resistance to external disturbances, stability, and low noise levels. Consequently, optical biosensors demonstrate excellent performance and have found widespread application in various fields, such as clinical diagnostics, drug discovery, food process control, and environmental monitoring [56–58]. However, the literature shown in Table 2 indicates limited applications of optical biosensors for non-invasive measurements, with most developments focusing on surface plasmon resonance (SPR) and fluorescence as transduction techniques [59].

3.1. Surface plasmon resonance (SPR)

Surface plasmon resonance (SPR) and Localized Surface Plasmon Resonance (LSPR) are real-time, label-free optical techniques that detect and quantify molecular interactions. SPR biosensors use surface plasmon waves (which are electromagnetic) to detect changes when the target analytes interact with the immobilized bioreceptors on the sensors' metallic surface [71]. LSPR uses electron oscillations in metal nanoparticles to detect low-concentration analytes through changes in localized electromagnetic fields. When there is a binding event between the analytes and the bioreceptors, it generates a change in the refractive index at the surface of the sensor. This change produces a variation in the propagation constant of the surface plasmon waves, which can be detected using a spectrophotometer [71,72]. These properties make SPR and LSPR valuable for developing sensitive and versatile biosensors for biomedical applications [73,74]. Especially, SPR-based biosensors are valuable for providing insights into non-covalent interactions of biomolecules, making them suitable for studies involving protein-protein or protein-small molecule interactions such as enzyme-substrate, antibody-antigen, protein-nucleic acids, and protein-polysaccharides [75–77]. They allow real-time, continuous monitoring of interaction processes, allowing for highly automated equipment for routine analysis without training. They also provide rapid results with high sensitivity and are extremely suitable for label-free detection.

SPR has a wide range of applications in biomedical research. For example, a SPR biosensor using lectin as a bioreceptor was developed for the rapid detection of Escherichia coli (E. coli) O157:H7 (Fig. 10) [61]. In this work, sensor chip CM5 was modified with 5 types of lectins: T. vulgaris (WGA), C. ensiformis (ConA), U. europaeus (UEA), A. hypogaea (PNA), M. amurensis (MAL). Different concentrations of *E. coli* were flowed through the chip for direct detection. These sensing platforms successfully detect *E. coli* O157:H7 from 3.0×10^3–3.0×10^8 cfu mL^{-1} with a 3×10^3 cfu mL^{-1} detection limit. The results from multiple lectins also indicated that different lectins exhibited different affinities with various bacteria and gave diverse SPR responses. The method was also conducted

Table 2
Optical measuring methods applied in lectin-based biosensors.

Optical methods	Sensing platform	Application	Target	Lectin	Limit of detection (LOD)	Detection range	Ref
SPR	Sensor chip CM5	Bacteria detection	Listeria monocytogenes	WGA	3.25 log CFU/100 μl	3.25 log counts/100 μl–7.4 log counts/100 μl	[60]
SPR	Sensor chip CM5	Bacteria detection	Escherichia coli O157: H7	WGA, ConA, UEA, PNA, MAL	3×10^3 cfu mL^{-1}	3.0 10^3–3.0 10^8 cfu mL-1	[61]
SPR	Polydopamine (PDA)	Glucose detection	D-glucose	ConA	10^{-7} M	10^{-7} to 10^{-4} M	[62]
SPR	Sensor chip CM5	Wide range	Multiple glycoproteins	LCA, MAL, SNA, AAL, ConA, PNA	0.01 mg mL^{-1}	0.01–1.0 mg mL^{-1}	[63]
Fluorescence	ZnO nanorod	Bacteria detection	Escherichia coli	ConA	1.0×10^3 CFU mL^{-1}	1.0×10^3 to 1.0×10^7 cfu mL^{-1}	[64]
Fluorescence	Quartz surface	Glucose detection	Glucose	ConA	NA	0–40 mM	[65]
Fluorescence	europium (III)-doped nanoparticles (Eu+3-NPs)	Breast cancer detection	CA15-3	WGA, MGL	less than 1 U/mL	1–1000 U/mL	[66]
Fluorescence	Fluoro-microbead guiding chip (FMGC)	Breast cancer detection	CA15-3	PNA, SNA	1.2 and 0.4 U/mL respectively	0.4 U/mL - 25 U/mL	[67]
Colorimetric	Gold nanoparticles (AuNPs)	Bacteria detection	*Staphylococcus aureus*	WGA	3.5×10^0 CFU/mL	3.5×10^0 CFU/mL – 3.5×10^5 CFU/mL	[68]
Colorimetric	Gold nanoparticles (AuNPs)	Bacteria detection	Escherichia coli O157: H7	ConA	41 CFU/mL	10^3–10^6 CFU/mL	[69]
SERS	Gold nanoparticles (AuNPs)	Bacteria detection	*Escherichia coli* 8739	ConA	103 CFU/mL		[70]
RIFTS	Porous silicon (PSi)	Bacteria detection	*Escherichia coli* and *Staphylococcus aureus*	ConA, WGA, UEA	10^3 cells mL^{-1}	10^3 to 10^5 cells mL^{-1}	[9]

with food samples, with the detection limit for E. coli O157:H7 contaminated cucumber samples and ground beef samples being 3.0×10^4 cfu mL^{-1} and 3.0×10^5 cfu mL^{-1}, respectively. This result demonstrated the possibility of utilizing the biosensor to detect bacteria in complex food samples.

Also, using sensor chip CM5, Safina et al. modified the chip with various types of lectins to detect multiple glycoproteins [63]. The assay of the glycoproteins was based on their binding with lectins, followed by SPR detection. Quantitative analysis was conducted, and the results of three pairs of glycoprotein-lectin were showcased: fetuin–LCA, thyroglobulin–LCA, and transferrin–SNA. Good linearity for all three glycoproteins in the concentration range of 0.01–1.0 mg mL^{-1} was observed, indicating the capability of the sensor to carry out the label-free detection of glycoproteins within a broad concentration range.

Utilizing a different sensing platform of polydopamine (PDA), modified with conA, Lobry et al. fabricated a non-enzymatic optical fiber-based sensor for D-glucose biosensing [62]. This study combined tilted fiber Bragg gratings (TFBGs) with the polyvalent binding PDA and the ConA specific affinity for D-glucose. The sensitivity of the biosensor is ideal for the D-glucose concentration in PBS ranging from 10^{-6} to 10^{-4} M, which is suitable for numerous medical detection purposes. The LOD was estimated to be close to 10^{-7} M. The obtained experimental sensitivity highlights the potential of using the sensing platform for medical diagnosis at an early stage.

Despite the advantages of SPR biosensors, they still have some limitations, including the high cost of sensor devices and chips, non-specific binding of target to non-sensor surfaces, quality of immobilization affects sensor performance, steric hindrance related to binding events, Complex data analysis, and limited evanescent wave penetration depth [31].

3.2. Fluorescence-based biosensors

In fluorescence-based biosensors, when the analytes bind with the sensors, the fluorescence intensity change is measured, and thus, the molecules are identified and quantified. For example, Zheng et al. proposed a lectin-functionalized ZnO nanorod (ZnO-NR) array-based sensors for E. coli detection [64]. In this work, ConA was immobilized on the 3D ZnO-NR surface to capture *E. coli* stained with DAPI through multivalent binding to polysaccharides on the surface of the bacterial cells. The results showed that the fluorescence intensity of bacteria captured by lectin functionalized 3D ZnO-NR arrays is linearly proportional to the *E. coli* concentration from 1.0×10^3 to 1.0×10^7 cfu mL^{-1}, with the LOD of 0.9×10^2 cfu mL^{-1}. The method was also used to detect different concentrations of *E. coli* spiked in seawater, and similar fluorescent intensity was obtained compared with *E. coli* in reaction buffer.

Fluorescence-based biosensors can also be used to detect cancer biomarkers. Park et al. successfully developed an antibody–lectin sandwich assay to detect CA15-3, a cancer antigen expressed on the surface of breast cancer cells [67]. In the study, Sambucus nigra agglutinin (SNA) and peanut agglutinin (PNA) lectins were conjugated with fluoro-microbeads and used as a detection molecule for the assay. A fluoro-microbead guiding chip (FMGC) containing multiple sensing and fluidic channels was designed to measure CA15-3 proteins (Fig. 11(a and b)). The PNA assay exhibited a correlating response over the 1.25–50 U/mL CA15-3 concentration range. The LOD of the developed assay was 1.2 U/mL, which was lower than that of the commercially available ELISA kit (3.0 U/mL). It is possible to obtain an accurate measurement of CA15-3 from the assay within 20 min, while the conventional ELISA needs more than 120 min. The SNA assay essentially brought relatively similar results. However, the linear detection range was narrower compared to the PNA-based assay. The LOD in the linear detection range was calculated to be 0.4 U/mL, 3 times lower than the PNA assay. Overall, the results showed that the newly developed assay could be a promising alternative to the typical antibody–body sandwich assay.

Also, using the approach of targeting the breast cancer biomarker CA15-3, Terävä et al. reported a sensing platform using europium (III)-doped nanoparticles (Eu^{+3}-NPs) coated with different lectins [66]. The CA15-3 was detected by measuring the time-resolved fluorescence of Eu. After lectin screening, MGL and WGA were selected for further analysis using clinical samples. The analytical performance of the assays was first tested using a BC-CA15-3 in a range of concentrations from 1 to 1000 U/mL. Saturation was not

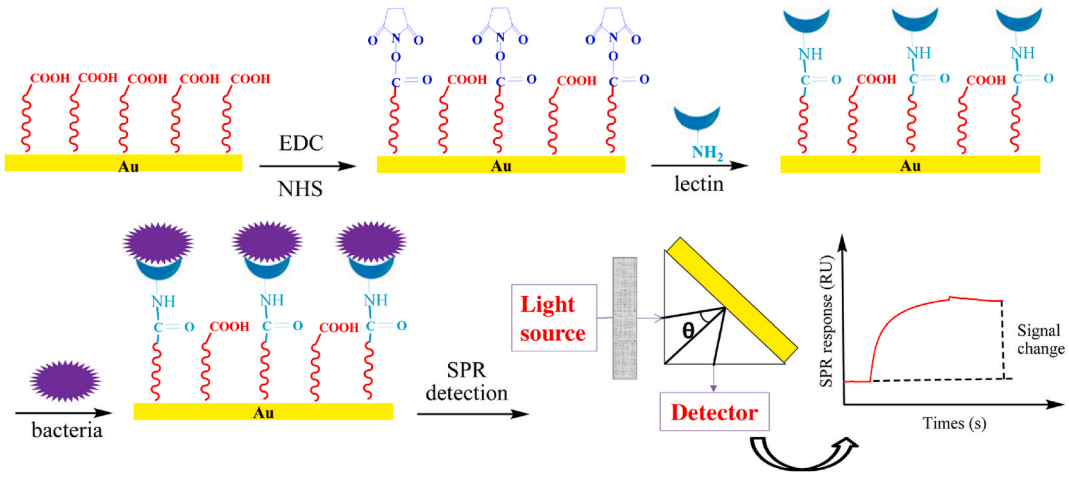

Fig. 10. Scheme of the lectin-based surface plasmon resonance biosensor for E. coli O157:H7 detection. Reproduced with permission from Elsevier, order number 5742820093085 [61].

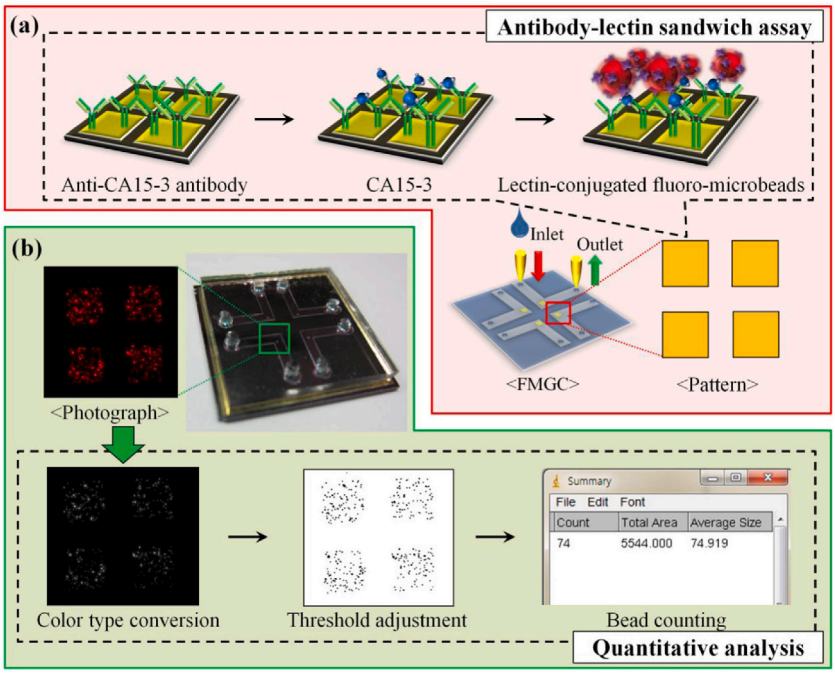

Fig. 11. Design of a fluoro-microbead guiding chip (FMGC) and Quantitative analysis of fluorescence images obtained from FMGC. Reproduced with permission from Elsevier, order number 5742820701158 [67].

observed at 1000 U/mL. A linear response was observed at a maximum of 125 U/mL, and the LOD was less than 1 U/mL. The assays were then used to assess plasma samples, which exhibited high sensitivity and the capability to distinguish metastatic breast cancer patients from health controls.

In summary, the major advantage of fluorescence-based biosensors lies in their high sensitivity, which enables the detection of low concentrations of biomolecules, often down to the single-molecule level. They also offer multiplexing capabilities, allowing simultaneous detection of multiple analytes. However, fluorescence biosensors face challenges such as photobleaching, background fluorescence from biological samples, and the need for careful calibration to minimize artifacts. Additionally, the requirement for labeling with fluorescent tags can introduce complexity and potentially alter the native state or behavior of the target molecules. In comparison, surface plasmon resonance (SPR) lectin-based biosensors offer a label-free detection method that directly measures changes in the refractive index at the sensor surface upon binding the analyte. SPR biosensors provide real-time kinetic data on binding events, such as association and dissociation rates, without requiring any external labels, which preserves the native state of the target molecules and reduces the risk of interference. This makes SPR biosensors particularly suitable for studying complex biomolecular interactions in their native environment. However, SPR biosensors are generally less sensitive than fluorescence-based sensors, especially for detecting very low concentrations of analytes. Additionally, the performance of SPR biosensors can be affected by the quality of the sensor surface, and they typically require expensive and sophisticated instrumentation. While fluorescence lectin-based biosensors excel in applications requiring high sensitivity and the detection of low-abundance targets, SPR lectin-based biosensors are advantageous for label-free detection and for studying the kinetics of molecular interactions in real time. The choice between these optical biosensing methods depends on the specific biomedical application. For example, fluorescence biosensors are often preferred for applications requiring multiplexing and the detection of low-concentration analytes, while SPR biosensors are more suitable for kinetic studies and when preserving the native state of biomolecules is critical. In conclusion, both types of biosensors offer unique advantages, and their use should be determined by the specific requirements of the intended biomedical application.

3.3. *Other optical techniques*

In addition to the above-mentioned methods, other optical methods were also applied to manufacture biosensors. Many were designed using the colorimetric method due to its various advantages. It typically provides simple and rapid detection, is portable and cost-effective, and does not require analytical equipment. However, there are significant drawbacks, such as limited quantification capability (since it is commonly just on-off detection) or low sensitivity [78]. To improve the sensitivity of the system, Yang et al. established a novel 2-step lectin-magnetic separation (LMS) method combined with gold nanoparticle (AuNPs) - based colorimetric system, using the magnetic nanoparticles (MNPs) for effective and low-cost bacteria enrichment [68]. Wheat germ agglutinin lectin from Triticum vulgaris (wheat) (WGA) was used to modify the system for detecting *Staphylococcus aureus* in blood samples. The AuNPs-based colorimetric system was performed with the concentrations of *S. aureus* in PBST between 3.5 CFU/mL–3.5 $\times$ 10^5

CFU/mL, and qualitatively, the color of the AuNPs solution changed from ruby-red to purple, gray visually with the increased concentration of bacteria. The experimental LOD in PBST was as low as 3.5 CFU/mL. The results also showed an excellent detection of *S. aureus* in the presence of interferences from the blood, suggesting the system's potential for clinical applications.

Surface-enhanced Raman scattering (SERS) is another optical method for lectin-based biosensors. With superior sensitivity, multiplexing capability, ability to characterize analyte in more detail, and free-label detection, SERS emerges as an excellent choice for the transducing method of the biosensor system. One disadvantage of SERS in comparison with other methods, however, is the limited quantification capability [78]. Nevertheless, Rahman et al. built a system consisting of ConA lectin-modified bacterial cellulose nanocrystals (BCNCs) for bacterial isolation and gold nanoparticles (AuNPs) for the detection of bacterial species [70]. The aggregated AuNP + bacteria + (conA + BCNC) conjugates generated SERS hot spots that enabled the SERS detection of the strain *Escherichia coli* 8739 at the 103 CFU/mL level.

In another study, reflectometric interference Fourier transform spectroscopy (RIFTS) was used for label-free and real-time detection of *E. coli* and *Staphylococcus aureus* (*S. aureus*) [9]. Meso-$PSiO_2$ was modified with three lectins of ConA (Concanavalin A), WGA (Wheat Germ Agglutinin), and UEA (Ulex europaeus agglutinin). The results showed a linear relationship between the FFT peak amplitude change percentage and bacterial concentration in the 3×10^3 to 3×10^5 cells mL^{-1} for 3 types of lectin modification and both types of bacteria. ConA was found to have the highest response to *E. coli*, and WGA was the best for *S. aureus* detection. LOD of about 10^3 cells mL^{-1} was observed for both ConA-*E. Coli* and WGA-*S. aureus* interaction platforms. By testing the biosensor with other bacteria, it can be concluded that WGA and ConA have a more robust interaction with Gram-positive and Gram-negative bacteria, respectively.

4. Other transduction methods

Electrochemical and optical are commonly used as transducer techniques; however, recently, some other transduction methods have been used to take advantage of each method. This paper will discuss Quartz crystal microbalance (QCM) and microfluidic biosensors.

QCM is a method of detection based on the change in mass. Therefore, it is ideally utilized for analytes with high molecular weight. In lectin-based biosensors, carbohydrate-lectin binding events would change the frequency of a quartz crystal resonator due to mass accumulation, as shown in Fig. 12 [79]. One advantage of the QCM is that it is a label-free method that measures minimal quality changes and monitors quality deposition in real time [20]. Pei et al. developed a QCM biosensor to study such interactions on the surface of mammalian cells [80]. Polystyrene-coated quartz crystals were modified with an epidermoid carcinoma cell line (A-431) and a breast adenocarcinoma cell line (MDA-MB-468) immobilized onto the surface. The binding and dissociation of lectins and the cells were monitored to gain insights into the complex recognition of cell glycoconjugates. This biosensor can be considered a novel tool to study cell surface glycosylation, potentially leading to more applications.

In another study, Li et al. reported the development of a QCM biosensor for analyzing carbohydrate-protein interactions on unfixed cancer cell surfaces [81]. Colon adenocarcinoma cells (KM-12) and ovary adenocarcinoma cells (SKOV-3) grew on the optimized polystyrene-coated biosensor chip. It was used to monitor the real-time association and dissociation between the cell surface carbohydrates and a range of lectins, including WGA, ConA, UEA-I, GS-II, PNA, and SBA. The thermodynamic and kinetic parameters of the interaction between lectins and cell surface glycan were also studied, which provided deep insight into the cell surface glycosylation and the complex molecular recognition on the intact cell surface.

Microfluidic biosensors become popular recently due to several features which make them appealing to clinical practices. In microfluidic devices, limited dimensions of flow channels enhance mixing through increased surface-to-volume ratio, thus ensuring efficient interaction between molecules. It also results in shorter diffusion time for molecules, leading to shorter reaction time. In addition, with microfluidics, a tiny volume of samples can be processed. However, this may also be a disadvantage of this method regarding sensitivity. For many clinical samples, the concentration of the analyte can be deficient, which requires very sensitive assays.

The microfluidic systems are not well-suited for handling large sample volumes, which is a disadvantage when only minimal sample volumes can be used. Optimization strategies are crucial to enhance the sensitivity of microfluidic assays. Intense research has been conducted on lectin-functionalized microfluidic assays for various biomedical applications. A study developed two innovative sandwich-based immunoassays for prostate cancer diagnosis within a microfluidic device, focusing on detecting free Prostate Specific

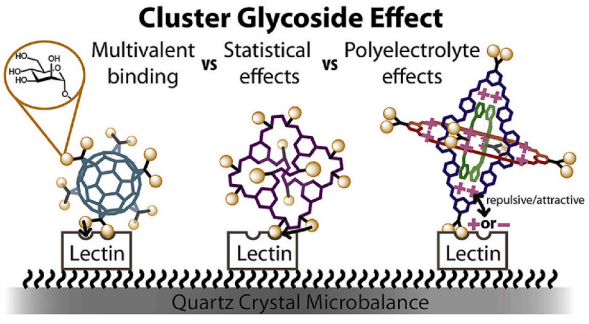

Fig. 12. QCM technique. Reproduced with permission from Elsevier, order number 5742820309075 [79].

Antigen (fPSA) [82]. In Fig. 13, these assays utilized a DNA aptamer in place of the primary antibody. They employed either a secondary antibody (Aptamer–Antibody Assay) or a lectin (Aptamer–Lectin Assay) to quantify the fPSA levels and their glycosylation status. Sambucus nigra (SNA) lectin was used in the Aptamer–Lectin assay, which demonstrated the potential to detect 0.5 ng/mL of fPSA and 3 ng/mL of glycosylated fPSA. This approach, applicable to various biomarkers, shows significant promise for medical diagnostics and prognosis.

Another microfluidic system for rapid and sensitive detection of *Salmonella* was reported [83]. The authors developed a highly sensitive nano biosensor based on isothermal amplification that combines microfluidic enrichment using a concanavalin A-functionalized microchannel with asymmetric herringbone groove arrays. The system demonstrated high sensitivity with a 5 CFU/mL LOD in urine samples. The whole experiment was conducted within 100 min, and remarkably, microfluidic enrichment improved the sensitivity by 1.76 orders of magnitude. This work has introduced an integrated microfluidic system that can perform an entire process to detect *Salmonella* on a single chip.

Despite these challenges discussed above, microfluidic lectin-based biosensors hold great promise for point-of-care diagnostics and personalized medicine due to their portability, rapid response times, and low sample requirements. Their integration with advanced detection methods, such as electrochemical or fluorescence-based readouts, further expands their versatility and applicability. However, for these sensors to achieve widespread clinical adoption, continued research is needed to address the issues of device fabrication, robustness, and reliability in diverse and complex sample matrices.

5. Challenges and future perspectives

As discussed above, lectin, a protein/glycoprotein capable of specifically binding to glycan structures, has been extensively used to fabricate biosensors to detect a wide range of biomolecules. Electrochemical and optical methods are favorable among different lectin-based biosensors for various advantages, such as high sensitivity, simple instrumentation, miniaturization capability, cost-effectiveness, and rapid detection. Through numerous studies and research, the methodology for designing and fabricating lectin-based biosensors has been well-established. Nevertheless, specific issues that require further investigation and improvement in future research are still presented. In particular.

1. Lectin-based biosensors have a short lifetime and can only be used within a few days after fabrication or stored in a buffer at 4 °C to preserve lectin. This lack of robustness can tremendously affect the ability to commercialize the sensor for mass utilization.
2. Most lectin-based biosensors are for single-use, which might be beneficial since it would reduce cross-contamination between samples. However, it would also increase the number of sensors needed, increasing the construction cost.
3. Since electrochemical and optical methods are mainly used, portability becomes an issue since these methods still require the sensors to be connected to large instruments to perform measurements. Essentially, more effort should be put into developing devices that allow portability.
4. The biggest issue with lectin-based sensors would probably be specificity. Lectins cannot be as specific as antibodies, DNA aptamers, or probes. Therefore, applying strategies that can improve the sensor's specificity is essential. One solution is that lectin can be used with other bioreceptors, such as antibodies, or multiple lectins can be used. For complex and heterogeneous conditions like cancer, the biosensor can integrate many lectins to detect a profile of glycan structures for a certain type of cancer to maximize selectivity and sensitivity. Another approach is identifying new carbohydrate biomarkers highly specific for a certain type of cell or pathogen.

Research in the biosensor field is growing fast; however, only a few can be applied in the real world. So far, numerous studies have been published demonstrating new sensing platforms with a wide range of materials, bioreceptors, biomarkers, and applications. Still, very few products were successfully developed and utilized in real-life contexts. The limited success of lectin-based biosensors in real-life biomedical applications can be attributed to several challenges inherent to their design, performance, and practical implementation, as discussed above. The major issue is still the specificity and selectivity of lectins. While lectins are valuable for their ability to bind specific carbohydrate structures, they often have broad binding profiles that can lead to cross-reactivity with non-target molecules, reducing the sensor's accuracy and reliability. Additionally, the immobilization of lectins onto sensor surfaces can compromise their binding activity and stability, especially over extended periods or under varying environmental conditions. Another significant barrier is the inherent variability of biological samples, such as blood or tissue fluids, which can introduce a wide range of interfering substances that affect the biosensor's performance. Furthermore, the translation of lectin-based biosensors from the laboratory to clinical settings has been limited by the complexity and cost of production, the need for specialized detection instruments, and the lack of standardized protocols, which collectively hinder large-scale manufacturing and commercialization. To overcome these limitations and promote the successful development and utilization of lectin-based biosensors in real-world contexts, several strategies and future research directions are proposed. First, enhancing the specificity of lectins through genetic engineering or the selection of recombinant lectins with more precise carbohydrate-binding properties could minimize cross-reactivity and improve sensor accuracy. Second, optimizing immobilization techniques, such as using nanomaterials or advanced surface chemistries, can help maintain the functional integrity and stability of lectins on sensor surfaces. Additionally, incorporating antifouling coatings or microfluidic systems can mitigate the impact of complex biological matrices by minimizing non-specific binding and fouling. To facilitate clinical translation, efforts should be directed toward developing portable, low-cost, and easy-to-use detection platforms that can be integrated into existing point-of-care diagnostic devices. Lastly, standardizing fabrication processes and establishing regulatory guidelines will be crucial for advancing the commercial viability of these sensors. Future work should focus on interdisciplinary collaboration between

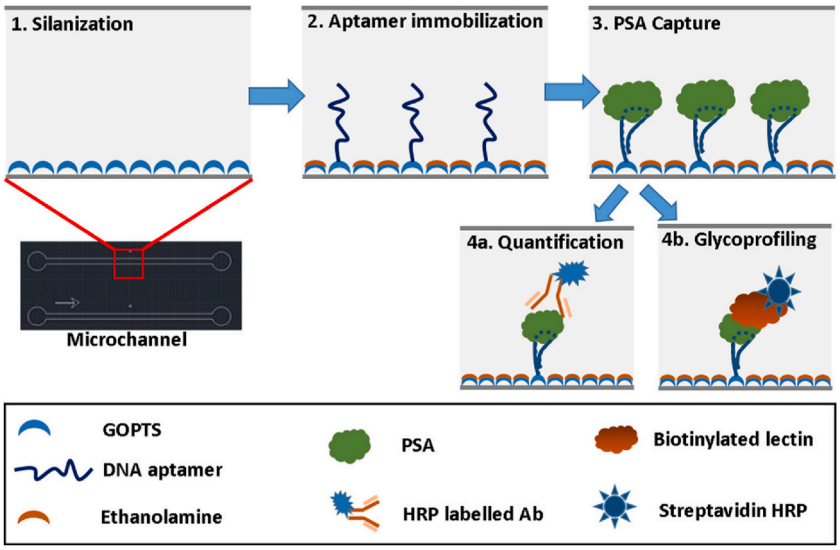

Fig. 13. Schematic representation of the microfluidic channel fabrication process. Reproduced with permission from Elsevier, order number 5742821499692 [82].

biochemists, engineers, and clinicians to refine lectin-based biosensor designs, validate their performance in diverse clinical scenarios, and ultimately pave the way for their broader adoption in healthcare settings.

Data availability statement

No data was used for the research described in the article.

Ethical statement

This study did not involve any human participants, animals, or sensitive data that would necessitate ethical approval. The nature of the research is to provide A comprehensive review on transduction methods of lectin-based biosensors in biomedical applications, and as such, it falls outside the purview of Ethics Committee requirements for ethical review and approval. All procedures and methodologies employed in this study adhere to the ethical standards of scientific research and publication.

CRediT authorship contribution statement

Tuyet Ngoc Linh Pham: Writing – original draft, Formal analysis, Data curation. **Son Hai Nguyen:** Writing – review & editing, Visualization, Formal analysis. **Mai Thi Tran:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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